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Synthesis of New Substituted Pyrrolo[2,3-b]- and Pyrrolo[3,2-a]acridinone Derivatives

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SYNTHESIS OF NEW SUBSTITUTED PYRROLO[2,3-*b*]- AND PYRROLO[3,2-*a*]ACRIDINONE DERIVATIVES

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Abstract : The synthesis of new pyrrolo [*a*]- and [*b*]acridinones by cyclization of N-arylindoles obtained using ultrasonic irradiations from nitro indole is reported.

Acridines are well known therapeutic agents thanks to their wide range of pharmacological and biological activities[1]. Similarly, the indole skeleton can be found in the literature as part of many biological molecules[2]. Therefore, with the wealth of our knowledge about acridinic tetracycles synthesis[3], we turned our attention towards the preparation of tetracycles bearing a pyrrolic ring fused to an acridinone moiety.

Our approach to pyrroloacridinone derivatives (**6-9**) (scheme 1) was based on the N-arylation of the primary aromatic amines **4a** and **4b** followed by cyclization with PPA.

First, 5-nitroindole **1** and 6-nitroindole **2** were methylated with methyl iodide in

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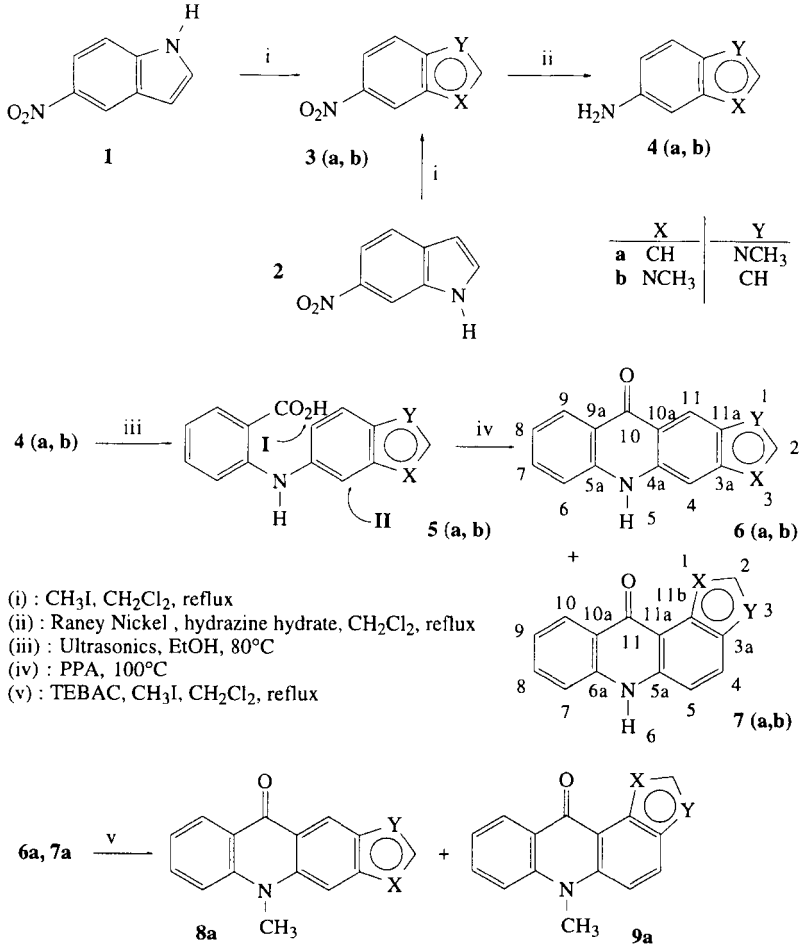

SCHEME 1

order to avoid an unsuccessful separation of the final "bent" and linear isomers[4] obtained from unmethylated pyrrole. 1-Methyl-5-nitroindole **3a** and 1-methyl-6-nitroindole **3b** were then reduced with Raney Nickel and hydrazine hydrate[5] to afford amino-1-methylindoles **4a** and **4b** with better yields (65 and 90 % respectively), than those obtained by reduction with stannous chloride in acidic methanol, (30 and 20% yield).

The next step was the arylation of the primary amine moiety in order to obtain the corresponding diarylamino derivatives **5a** and **5b**. N-arylanthranilic acids are usually prepared by Ullman-Goldberg condensation[6] with yields of 40-50 %, but we prooved recently that the use of ultrasonic irradiations during the condensation step, (kinetically determining in our synthesis pathway), could led to a significant increase in yield[7]. Furthermore this method saves having to use high boiling point solvents, (such as pentanol), and allows the anthranilic acids to be isolated more easily. We obtained in this case 60% for **5a** and 73% for **5b**.

In both cases, two isomers can be formed depending on the cyclization positions I or II (scheme 1) in anthranilic acids **5a** and **5b**. For example ring cyclization on I (**5a**, 6-C) will conduce to the linear [*b*] isomer **6a**, while reaction on II (4-C) will led to the "bent" [*a*] isomer **7a**.

We obtained effectively in PPA a mixture of both isomers **6a** + **7a** which were separated by chromatography (43% for linear **6a** and 39% for his homologue **7b**). Moreover, despite the fact that this separation was slow and quite difficult, the N-methylation of the mixture (**6a** + **7a**) before PPA use allowed us to obtain easily the two derivatives **8a** and **9a** only by crystallization from alcool, (42 and 40% respectively).

The difficulties encountered throughout the separation processes led us to think that use of N-(1-methylindol-6-yl)anthranilic acid **5b** could afford to the exclusive or quasi exclusive formation of the linear derivative **7b**. Thus, we obtained after chromatography separation the 3-methylpyrrolo[3,2-*b*]-10(5*H*)-acridinone **6b** with 64% yield as the major product, while **7b** was recovered with only 16% yield.

The structure of compounds **6-9** was unambiguously established by ^{1}H and ^{13}C NMR spectroscopy using both direct and long-range heteronuclear correlation experiments (HMQC and HMBC sequences[8]). Structural discrimination between the two isomers resulted from the multiplet pattern of the C-ring protons, in

particular H-4 and H-11 which resonated as two singlets in the case of a [*b*] fusion (for example 7.65 and 8.30 ppm for linear **6a**; while two doublets characteristics of an AB system were observed at 7.92 and 7.34 ppm for **7a** ([*a*] fusion).

In conclusion, we reported the preparation of a new class of heterocycles, the pyrrolo[*a*]- and [*b*]acridinones, by means of ultrasonic irradiations. This synthetical approach could presumably contribute to the preparation of other tetracyclic derivatives.

EXPERIMENTAL :

All melting points were obtained using a Mettler FP 61 and are given herein uncorrected. ^{1}H and ^{13}C spectra were recorded on a Bruker AMX-400 spectrometer in DMSO-d_6; chemical shifts are reported in parts per million (δ) with reference to TMS (as internal standard). Standard pulse sequences HMBC and HMQC were used for heteronuclear correlation experiments. 5-nitroindole **1** was purchased from Lancaster. 6-nitroindole **2** was prepared according to reference 9.

1-Methyl-5-nitroindole (3a)

Methyl iodide (3.4 g, 24 mmol) was slowly added at room temperature to a mixture of 5-nitroindole **1** (2 g, 12.3 mmol), potassium hydroxide (2 g, 35.6 mmol), water (5 ml) and acetone (20 ml). After 20 mn, the obtained precipitate was filtered. The residue was dissolved in dichloromethane (30 ml) and washed with water (3x20 ml). The organic layers were dried over anhydrous sodium sulfate, evaporated under reduce pressure to afford compound **3** (1.86 g, 96 %); mp 166°C (MeOH). Anal. Calcd for $C_9H_8O_2N_2$: C, 61.36; H, 4.55; N, 15.91. Found: C, 61.41; H, 4.63; N, 15.84. ^{1}H -Nmr δ : 3.86 (CH_3, s), 6.72 (1H, d, J = 3.2 Hz), 7.59 (1H, d, J = 3.2 Hz), 7.61 (1H, d, J = 9.4 Hz), 8.02 (1H, dd, J = 2.3; 9.4 Hz), 8.55

(1H, d, J = 2.3 Hz). ^{13}C-Nmr δ : 32.92 (CH_3), 103.28 (3-C), 110.15 (7-C), 116.23 (4-C), 117.39 (6-C), 127.15 (3a-C), 133.43 (2-C), 139.16 (5-C), 140.60 (7a-C).

5-Amino-1-methylindole (4a)

Hydrazine hydrate (15 ml, 31 mmol) in methanol (30 ml) was added slowly to a solution of 1-methyl-5-nitroindole **3a** (3 g, 17 mmol) and Raney Nickel (2 g) in methanol (60 ml). The mixture was kept under stirring at room temperature until it became colorless. Next, the free amine was obtained by pouring the solution into a large excess of water. The precipitate was isolated and dried, recrystallized from EtOH/H_2O (95/5) to give **4a** (1.63 g, 65 %); mp 105°C (EtOH/H_2O). Anal. Calcd for $C_9H_{10}N_2$: C, 73.97; H, 6.85; N, 19.18. Found: C, 73.84; H, 6.94; N, 19.03. ^{1}H-Nmr δ : 3.66 (CH_3, s), 4.48 (NH_2, s), 6.11 (1H, d, J = 3 Hz), 6.55 (1H, dd, J = 1.9; 8.6 Hz), 6.69 (1H, d, J = 1.9 Hz), 7.08 (1H, d, J = 3 Hz), 7.09 (1H, d, J = 8.6 Hz). ^{13}C-Nmr δ : 32.31 (CH_3), 98.63 (3-C), 103.54 (4-C), 109.60 (6-C), 111.76 (7-C), 128.90 (2-C), 128.94 (7a-C), 130.57 (3a-C), 141.23 (5-C).

N-(1-methylindol-5-yl)anthranilic acid (5a)

A mixture of 5-amino-1-methylindole **4a** (3.5 g, 24 mmol), 2-bromobenzoic acid (5.78 g, 23 mmol), anhydrous K_2CO_3 (6.2 g, 0.11 mol), powdered copper (0.22 g) in ethanol (50 ml) was treated for 2h with ultrasonic irradiations (Trans-sonic 570/H at 35 kHz). The solvent was then evaporated. The residue was dissolved with hot water (60 ml), refluxed and then filtered. Acidification to pH = 5-6 with 1N HCl, led to N-(1-methylindol-5-yl)anthranilic acid **6a** as a greenish solid by filtration. Purification by chromatography on silica gel (Et_2O) gave product **5a**

(3.8 g, 60%); mp 225°C (Et_2O). Anal. Calcd for $C_{16}H_{14}O_2N_2$: C, 72.18; H, 5.26; N, 10.53. Found: C, 72.21; H, 5.33; N, 10.45. ^{1}H -Nmr δ : 3.78 (CH_3, s), 6.38 (1H, d, J = 3 Hz), 6.63 (1H, t, J = 7.8 Hz), 6;90 (1H, d, J = 8.5 Hz), 7.02 (1H, dd, J = 1.6; 8.6 Hz), 7.24 (1H, m), 7.33 (1H, d, J = 3 Hz), 7.40 (1H, d, J = 1.6 Hz), 7.44 (1H, d, J = 8.6 Hz), 7.86 (1H, dd, J = 1; 7.8 Hz), 9.52 (NH, s). ^{13}C-Nmr δ : 32.53 (CH_3), 100.19 (3-C), 110.48 (4-C), 110.70 (12a-C), 112.73 (6-C), 115.47 (9-C), 115.80 (7-C), 118.98 (11-C), 128.67 (7a-C), 130.39 (2-C), 131.46 (12-C), 131.83 (3a-C), 134.09 (15-C), 135.10 (5-C), 149.83 (8a-C), 170.15 (13-C).

1-Methylpyrrolo[2,3-*b*]-10(5*H*)-acridinone (6a) and 3-methylpyrrolo-[3,2-*a*]-11(5*H*)-acridinone (7a)

Compound **5a** (0.5 g, 2mmol) was stirred in PPA (5 g, 35 mmol) at 100°C for 2h and then cooled. The mixture of 1- and 3-methyl isomers was then filtered and dried to give **6a+7a** (0.43 g, 92%). Separation by chromatography on alumine with CH_2Cl_2/Ac_2O (95/5) as eluent. 3-Methylpyrrolo[3,2-*a*]-11(5*H*)-acridinone **7a** was eluted first, followed by 1-methylpyrrolo[2,3-*b*]-10(5*H*)-acridinone **6a**.

6a (0.20 g, 43%); mp 365°C (CH_2Cl_2/Ac_2O). Anal. Calcd for $C_{16}H_{12}ON_2$: C, 77.42; H, 4.84; N, 11.29. Found: C, 77.48; H, 4.84; N, 11.23. ^{1}H -Nmr δ : 3.90 (CH_3, s), 6.54 (1H, dd, J = 0.8; 3.1 Hz), 7.13 (1H, m), 7.48 (1H, d, J = 8.3 Hz), 7.65 (1H, s), 7.67 (1H, d, J = 3.1 Hz), 7.69 (1H, m), 8.23 (1H, dd, J = 1.5; 8.1 Hz), 8.30 (1H, s), 11.39 (NH, s). ^{13}C-Nmr δ : 32.84 (1-CH_3), 99.16 (3-C), 105.22 (4-C), 105.54 (11-C), 116.62 (6-C), 117.32 (10a-C), 118.51 (9a-C), 119.34 (8-C), 126.20 (9-C), 133.01 (7-C), 133.84 (3a-C), 133.90 (11a-C), 134.85 (4a-C), 136.19 (2-C), 141.38 (5a-C), 177.61 (10-C).

7a (0.18 g, 39%); mp 340°C (CH_2Cl_2/Ac_2O). Anal. Calcd for $C_{16}H_{12}ON_2$: C,

77.42; H, 4.84; N, 10.29. Found: C, 77.54; H, 5.04; N, 10.21. ^{1}H -Nmr δ : 3.92 (3-CH_3, s), 7.23 (1H, m), 7.34 (1H, d, J = 9.1 Hz), 7.48 (1H, d, J = 2.8 Hz), 7.56 (1H, d, J = 2.8 Hz), 7.59 (1H, m), 7.67 (1H, m), 7.92 (1H, d, J = 9.1 Hz), 8.28 (1H, dd, J = 1.2; 8 Hz), 11.74 (NH, s). ^{13}C-Nmr δ : 32.85 (3-CH_3), 103.22 (1-C), 111.12 (5-C), 113.03 (11a-C), 117.14 (7-C), 117.58 (4-C), 120.43 (9-C), 121.29 (10a-C), 123.97 (11b-C), 125.64 (10-C), 130.29 (2-C), 130.91 (3a-C), 132.09 (8-C), 137.36 (5a-C), 138.85 (6a-C), 177.99 (11-C).

1,5-Dimethylpyrrolo[2,3-*b*]-10-acridinone (8a) and 3,6-dimethylpyrrolo[3,2-*a*]-10-acridinone (9a)

The mixture of isomers **6a** and **7a** (0.52 g, 2 mmol) was treated with methyl iodide (0.5 g, 3.5 mmol), TEBAC (0.23 g, 1 mmol) with phase transfer catalysis in CH_2Cl_2 (25 ml) and a solution of KOH, (5.4 g, 96 mmol, in water (10 ml)). The solution was kept under stirring at 100°C for 24 h and cooled. The aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with water, dried over anhydrous sodium sulphate and evaporated. Crystallization of the residue from ethanol (20 ml) yielded the bent isomer **9a** immediatly, whereas the linear **8a** was obtained after 24h of cooling.

8a (0.23 g, 42%); mp 210°C (EtOH). Anal. Calcd for $C_{17}H_{14}ON_2$: C, 77.86; H, 5.34; N, 10.69. Found: C, 77.81; H, 5.28; N, 10.64. ^{1}H -Nmr δ : 3.87 (5-CH_3, s), 3.89 (1-CH_3, s), 6.56 (1H, dd, J = 0.9; 3.1 Hz), 7.21 (1H, m), 7.65 (1H, d, J = 3.1 Hz), 7.70 (1H, m), 7.71 (1H, m), 7.84 (1H, s), 8.33 (1H, m), 8.36 (1H, s). ^{13}C-Nmr δ : 32.71 (1-CH_3), 33.84 (5-CH_3), 99.85 (3-C), 104.63 (4-C), 106.27 (11-C), 115.22 (6-C), 119.23 (8-C), 119.64 (10a-C), 119.87 (9a-C), 126.61 (9-C), 133.10 (3a-C), 133.44 (7-C), 133.90 (11a-C), 135.98 (2-C), 136.41 (4a-C), 142.45 (5a-C), 177.30 (10-C).

9a (0.22 g, 40%); mp 260°C (EtOH). Anal. Calcd for $C_{17}H_{14}ON_2$: C, 77.86; H, 5.34; N, 10.69. Found: C, 77.83; H, 5.31; N, 10.72. ^{1}H -Nmr δ : 3.92 (3-CH_3, s), 4.02 (6-CH_3, s), 7.31 (1H, dt, J = 1.5; 7.9 Hz), 7.53 (1H, d, J = 2.9 Hz), 7.65 (1H, d, J = 9.3 Hz), 7.66 (1H, d, J = 2.9 Hz), 7.79 (1H, dd, J = 1.5; 6.7 Hz), 7.87 (1H, m), 7.99 (1H, d, J = 9.3 Hz), 8.40 (1H, dd, J = 1.5; 8 Hz). ^{13}C-Nmr δ : 32.70 (3-CH_3), 34.66 (6-CH_3), 103.47 (3-C), 109.61 (6-C), 115.88 (1-C), 117.37 (5-C), 120.43 (11a-C), 120.48 (4-C), 122.36 (10a-C), 124.48 (3a-C), 126.04 (7-C), 131.11 (10-C), 131.15 (9-C), 131.22 (11b-C),132.57 (8-C), 138.85 (5a-C), 141.31 (6a-C), 176.72 (11-C).

1-Methyl-6-nitroindole (3b)

1-Methyl-6-nitroindole was obtained by methylation of compound **2** (2 g, 12.3 mmol) as described above for the preparation of 1-methyl-5-nitroindole **3a**.

3b (2 g, 92%); mp 77°C (MeOH). Anal. Calcd for $C_9H_8O_2N_2$: C, 62.79; H, 4.65; N, 16.28. Found: C, 62.65; H, 4.64; N, 16.35.^{1}H -Nmr δ : 3.91 (1-CH_3, s), 6.62 (1H, dd, J = 0.8; 3 Hz), 7.70 (1H, d, J = 8.7 Hz), 7.73 (1H, m), 7.89 (1H, dd, J = 2.1; 8.7 Hz), 8.44 (1H, dbr, J = 2.1 Hz). ^{13}C-Nmr δ : 32.87 (1-CH_3), 101.51 (3-C), 106.84 (7-C), 113.95 (5-C), 120.45 (4-C), 132.86 (3a-C), 134.80 (7a-C), 136.20 (2-C), 141.85 (6-C).

1-Methyl-6-Aminoindole (4b)

1-Methyl-6-nitroindole **3b** (2 g, 14 mmol) was reduced as described above for the reduction of **3a** to afford **4b** as an oil (1.5 g, 90%). Anal. Calcd for $C_9H_{10}N_2$: C, 73.97; H, 6.85; N, 19.18. Found: C, 74.08; H, 6.81; N, 19.29.^{1}H -Nmr δ : 3.59 (1-CH_3, s), 4.70 (NH_2, s), 6.24 (1H, d, J = 2.8 Hz), 6.51 (1H, m), 6.52 (1H, m,), 6.94 (1H, d, J = 2.8 Hz), 7.26 (1H, d, J = 8.2 Hz). ^{13}C-Nmr δ : 32.11 (1-

CH_3), 93.32 (7-C), 100.21 (3-C), 109.78 (5-C), 119.91 (3a-C), 120.57 (4-C), 126.22 (2-C), 138.03 (7a-C), 143.90 (6-C).

N-(1-methylindol-6-yl)anthranilic acid (5b)

This acid was obtained as described above for the preparation of **5a**.

5b (4.7 g, 73%); mp 205°C (Et_2O) Anal. Calcd for $C_{16}H_{14}O_2N_2$: C, 72.18; H, 5.26; N, 10.53. Found: C, 72.21; H, 5.34; N, 10.59. ^{1}H -Nmr δ : 3.73 (1-CH_3, s), 6.68 (1H, t, J = 7.6 Hz), 6.40 (1H, d, J = 3 Hz), 6.94 (1H, dd, J = 1.8; 8.3 Hz), 7.11 (1H, d, J = 8.2 Hz), 7.24 (1H, d, J = 3 Hz), 7.30 (1H, m), 7.32 (1H, m), 7.53 (1H, d, J = 8.3 Hz), 7.91 (1H, dd, J = 1.5; 7.6 Hz), 9.71 (NH, s), 12.90 (COOH, s). ^{13}C-Nmr δ : 32.43 (1-CH_3), 100.46 (7-C), 104.50 (3-C), 111.21 (12a-C), 113.10 (5-C), 116.18 (9-C), 121.01 (11-C), 125.21 (4-C), 129.63 (12-C), 131.78 (2-C), 132.80 (3a-C), 134.16 (10-C), 134.30 (6-C), 137.05 (7a-C), 149.06 (8a-C), 170.20 (13-C).

3-Methylpyrrolo[3,2-*b*]-10(5*H*)-acridinone (6b) and 1-methyl pyrrolo[2,3-*a*]-11(6*H*)-acridinone (7b)

A mixture of **6b** and **7b** (0.75 g, 80%) was obtained by cyclization of **5b** (1 g, 3.8 mmol) as described above for the preparation of **6a** and **7a**. The isomers were separated by chromatography on silicagel with CH_2Cl_2/Ac_2O (70/30) as eluent. 3-Methylpyrrolo[3,2-*b*]-10(5*H*)-acridinone **6b** was eluted first, followed by 1-methylpyrrolo[2,3-*a*]-11(6*H*)-acridinone **7b**.

6b (0.6 g, 64%); mp 340°C (CH_2Cl_2/Ac_2O). Anal. Calcd for $C_{16}H_{12}ON_2$: C, 77.42; H, 4.84; N, 11.29. Found: C, 77.48; H, 4.82; N, 11.34. ^{1}H -Nmr δ : 3.83 (CH_3, s), 6.63 (1H, d, J = 3.3 Hz), 7.16 (1H, dt, J = 0.9; 7.6 Hz), 7.34 (1H, s), 7.46 (1H, d, J = 3.3 Hz), 7.49 (1H, d, J = 8.3 Hz), 7.67 (1H, dt, J = 0.9; 7.6

Hz), 8.24 (1H, d, J = 7.6 Hz), 8.52 (1H, s), 11.54 (NH, s). ^{13}C-Nmr δ : 32.74 (CH_3), 93.85 (4-C), 101.56 (1-C), 116.08 (10a-C), 116.63 (6-C), 118.39 (11-C), 119.05 (9a-C), 119.63 (8-C), 125.21 (11a-C), 126.23 (9-C), 132.54 (2-C), 133.00 (7-C), 137.08 (4a-C), 140.69 (3a-C), 141.42 (5a-C).

7b (0.15 g, 16%); mp 365°C (CH_2Cl_2/Ac_2O). Anal. Calcd for $C_{16}H_{12}ON_2$: C, 77.42; H, 4.84; N, 11.29. Found: C, 77.42; H, 4.82; N, 11.28. ^{1}H -Nmr δ : 4.22 (CH_3, s), 7.26 (1H, m), 7.42 (1H, d, J = 2.8 Hz), 7.43 (1H, d, J = 8.6 Hz), 7.46 (1H, d, J = 2.8 Hz), 7.59 (1H, m), 7.61 (1H, d, J = 8.6 Hz), 7.71 (1H, m), 8.23 (1H, dbr, J = 7.2 Hz), 11.90 (NH, s). ^{13}C-Nmr δ : 41.1 (CH_3), 100.83 (3-C), 103.15 (11a-C), 110.20 (5-C), 118.00 (3a-C), 118.06 (7-C), 118.15 (9-C), 122.64 (10a-C), 123.92 (4-C), 128.68 (2-C), 130.44 (10-C), 133.38 (8-C), 137.05 (5a-C), 138.57 (11b-C), 141.24 (6a-C), 176.23 (11-C).

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